II. REMARKS/ARGUMENTS

A. Status of Claims

Claims 56 and 57 have been amended without prejudice. Support for the amendments to claim 56 can be found, e.g., on page 22, lines 5-22, of the original specification. Support for the amendments to claim 57 can be found, e.g., on page 25, lines 16-17, of the original specification.

New claims 66 and 67 have been added. Support for new claims 66 and 67 can be found, e.g., on page 18 of the original specification.

Status identifiers for claims 50, 57-58 and 65 have been changed from "withdrawn" to "previously presented," because the Requirement for Species Election mailed on June 4, 2008, was withdrawn. *Office Action, page 2.*

Claims 1-37 and 39-46 were previously cancelled without prejudice.

Claims 38 and 47-67 are currently pending, and are encompassed by the elected invention and the elected species.

B. Information Disclosure Statement

In the Office Action, it was indicated that "[t]he IDS filed on November 19, 2007 was considered."

Applicants note that a copy of the Form PTO-1449 returned with the Office Action does not contain Examiner's initials next to reference AG. Applicants respectfully request that reference AG be considered by the Examiner, and a copy of Form PTO-1449 containing Examiner's initials be returned to the undersigned attorney. For the Examiner's convenience, a duplicate copy of the Form PTO-1449 is attached to this response as Appendix A.

C. 35 U.S.C. §103 Rejection over U.S. Patent No. 4,569,937 to Baker et al.; Friedel et al. (Drugs, 1993. Vol. 45(1), pp. 131-156); and Eversmeyer et al. (American Journal of Medicine, Aug. 1993, Vol. 95, pp. 10S-18S).

Claims 38, 47, 48, 50-52, 62 and 63 were rejected under 35 U.S.C. § 103(a) over U.S. Patent No. 4,569,937 to Baker et al. ("the Baker patent"); Friedel et al. (Drugs, 1993. Vol. 45(1), pp. 131-156); and Eversmeyer et al. (American Journal of Medicine, Aug. 1993, Vol. 95, pp. 10S-18S). The Examiner stated that "one of ordinary skill in the art would have been motivated to substitute nabumetone and/or pharmaceutical salt thereof (a NSAID) for ibuprofen (a different NSAID) in the Baker reference compositions in light of the Friedel and/or Eversmeyer reference teachings that nabumetone is equally efficacious, but is safer with less side effects (e.g. as compared to ibuprofen)." *Office Action, page 7.*

The rejection is traversed, because the cited references do not teach that nabumetone is safer than ibuprofen, and do not provide a reason for one skilled in the art to substitute ibuprofen of the Baker's compositions with nabumetone.

In response to the Examiner's reliance on KSR, 127 S. Ct. at 1741, Applicants note that, in KSR, the Court acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *See KSR, 127 S.Ct. at 1731.*

The Board of Patent Appeals and Interferences has recently confirmed that:

> ... obviousness cannot be proven merely by showing that the elements of a claimed device were known in a prior art; it must be shown that those of ordinary skill in the art would have had some "apparent reason to combine the known elements in the fashion claimed ...
> [Similarly,] obviousness cannot be proven merely by showing that a known composition could could have been modified by routine experimentation or solely on the expectation of success; it must be shown that those of ordinary skill in the art would have had some apparent reason

> to modify the known composition in a way that result in the claimed composition.

Appeal No. 2007-4423, Decision of Appeal dated July 23, 2008.

The reason advanced by the Examiner in the present case (i.e., that nabumetone is safer than ibuprofen) is not supported by the cited references. To the contrary, Eversmeyer teaches that incidence of certain side effects (i.e., diarrhea) is higher with nabumetone, as compared to ibuprofen. *Eversmeyer, pages 2A-12S to 2A-13S (diarrhea "occurred* ***in more*** *(p<0.003) patients treated with nabumetone (7%) than in patient treated with ... ibuprofen (0.9%) ... ").*

The fact that Eversmeyer associates nabumetone with higher incidence of diarrhea should be considered by the Examiner as evidence of dissuading away from substituting ibuprofen with nabumetone in the Baker's compositions. *See, e.g., Takeda v. Alpharm, 492 F.3D 1350 (C.A. Fed. 2007)*[1].

It shall also be noted that Table II on page 12S of Eversmeyer shows that incidence of constipation was higher in patients receiving nabumetone than ibuprofen (1.7 % for nabumetone versus 0.9% for ibuprofen). Because constipation is a side effect associated with oxycodone (see, e.g., Appendix A submitted with the response filed on June 11, 2007), the teaching of Eversmeyer of increased incidence of constipation with nabumetone (as compared to ibuprofen) would further dissuade a skilled person from substituting ibuprofen with nabumetone in the Baker's compositions, because of nabumetone's potential to exacerbate the side effect of oxycodone (i.e., constipation).

In response to the Examiner's reliance on the KSR's statement that "the fact that a combination was obvious to try might show that it was obvious under § 103," Applicants

[1] In Takeda, the cited reference (Sodha II) stated that a certain compound (i.e., compound b) caused "considerable increases in body weight and brown fat weight." The conclusion of the Court was that "one of ordinary skill in the art would have concluded that Sodha II taught away from [certain compounds (i.e., pyridyl compounds)] ... because it associated adverse side effects with the compound b," which was encompassed by the genus of the pyridyl compounds. *Takeda at 1359.*

note that in KSR this statement referred to a situation where "there are a **finite** number of identified, predictable solutions." See KSR, 127 S. Ct. at 1732 (emphasis added).

This is not the case in the present rejection. According to the Examiner, the teachings of Baker are not limited to combinations of opioids with ibuprofen, and purportedly include combinations of opioids with "different (functionally equivalent) NSAIDs." How many other ibuprofen functionally equivalent NSAIDs are there?

If the Examiner's interpretation of Baker is correct (a position which is traversed), the present case "fails to present the type of situation contemplated by the Court when it stated that an invention may be deemed obvious if it was "obvious to try,"" because, based on the Examiner's interpretation, the number of NSAIDs is not finite. *See Takeda at 1359.*

Applicants respectfully reiterate that nabumetone is not an equivalent of ibuprofen, because the chemical structure, physical properties and pharmacokinetic parameters of nabumetone are different than those of ibuprofen. Applicants also reiterate that the "selected NSAID" of Baker is ibuprofen, and does not include nabumetone.

In response to the Examiner's assertion that Eversmeyer teaches that nabumetone was "shown to be more safe, with reduced side-effects ...," Applicants note that a percentage of patients experiencing "at least one adverse effect that was considered by the investigator to be related or probably related to therapy" **was lower** (33.3% compared to 25.5%) in patients treated with nabumetone than with ibuprofen in the study described in Eversmeyer. *Eversmeyer, page 2A-12S.* In other words, according to Eversmeyer, a patient treated with nabumetone was more likely to experience at least one side effect related to therapy, as compared to a patient treated with ibuprofen.

Furthermore, diarrhea "occurred **in more** ($p<0.003$) patients treated with nabumetone (7%) than in patient treated with ... ibuprofen (0.9%) ...." *Eversmeyer, pages 2A-12S to 2A-13S.*

The percentage change from baseline in GI distress was also not lower in patients receiving nabumetone, as compared to patients receiving ibuprofen. *Eversmeyer, page 2A-15S ("the percent change from baseline in GI distress was 14% with both nabumetone and ibuprofen").*

Regarding the incidence of ulcers, Applicant note that the two patients in the ibuprofen treated group that developed ulcers during the study in Eversmeyer both had a history of gastric problems ("GI upset" or "GI bleed"). Therefore, it is improper to conclude based on this portion of Eversmeyer that these patients would not have developed ulcers had they been treated with nabumetone and not ibuprofen.

Friedel also does not establish that nabumetone is safer than ibuprofen. Friedel states that "it is as yet unclear whether it [nabumetone] an advantage in this regard [i.e., having a lower potential for producing bleeding] ...." *Friedel, page 151.* Friedel further states that "[f]urther postmarketing surveillance studies would be needed to clarify the safety of nabumetone in terms of gastrointestinal bleeding relative to other NSAIDs in common use." *Id.* In response to the Examiner's statement that Friedel teaches that nabumetone "produced a lower incidence of gastrointestinal erosions or microbleeding than ... ibuprofen", Applicants note that "the incidence of gastrointestinal symptoms *[in Friedel]* attributed to nabumetone was comparable with that of ... ibuprofen ...," rather than lower. *Friedel, page 150.*

Regarding the physician-assessed degree of recovery, Friedel states that "ibuprofen was **superior** to nabumetone ..." *Friedel, page 147 (emphasis added).*

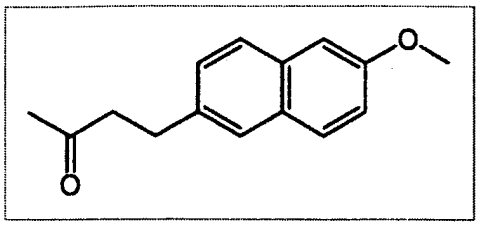
Regarding comparative efficacy of nonulcer adverse events between nabumetone and ibuprofen, Friedel implies that the incidence of these adverse events was not lower with nabumetone, as a recent study "identified similar rates of discontinuation of treatment because on nonulcer adverse events in the nabumetone and ibuprofen

monotherapy groups (5 and 4% respectively). *Friedel, page 151.*

For the foregoing reasons, the combination of the Eversmeyer and Friedel references does not establish that nabumetone is a safer alternative to ibuprofen. Moreover, the chemical structure, physical properties and pharmacokinetic parameters of nabumetone are different from ibuprofen's. The combination of the cited references does not therefore provide a reason for one skilled in the art to substitute ibuprofen with nabumetone in the Baker's compositions.

In response to the Examiner's statement that "the instant situation is amenable to the type of analysis set forth In re Kerkoven, 205 USPQ 1069 (CCPA) wherein the court held that it is prima facie obvious to combine to (or more) compositions each of which is taught by the prior art to be useful for the same person," Applicants note that these are not the facts in the present case. In Kerkoven, the invalidated claims merely combined the two compositions, in order to form a third composition. In the present case, the modification suggested by the Examiner does more—it substitutes one ingredient for another, rather than merely combine two compositions to form a third composition. Applicants therefore submit that Kerkoven is inapplicable to the present case.

In response to the Examiner's statement that the purpose of Baker is "to make and use pharmaceutical compositions with various combinations of narcotic analgesics and NSAID so that synergistic and/or additive effects of the combinations of the drugs can be utilized," Applicants note portion of the Baker reference relied upon by the Examiner discusses U.S. Patent No. 4,464,376 to Sunshine et al. The Sunshine reference is directed to combination of "a **selected** NSAID and a selected narcotic analgesic" (emphasis added). Nabumetone is not part of the "selected NSAIDs" described in the Sunshine reference, at the very least because nabumetone is not mentioned in the Sunshine reference. In this regard, Applicants note that the chemical structure for nabumetone provided on page 8 of the response filed on June 11, 2007 was incorrect. The correct structure of nabumetone is:



In response to the Examiner's statement that "the Baker teaching includes Baker's entire specification and claims, inclusive of Baker's summary of the state of the prior art," Applicants respectfully reiterate that nabumetone is not mentioned anywhere in Baker, including the references in the Background Section of Baker.

In response to the Examiner's statement that "the combination of the cited references "substitutes" ibuprofen for nabumetone to achieve the predictable synergistic effects, as taught or evidenced by the cited references," Applicants respectfully note a synergistic effect between nabumetone and oxycodone is not suggested by the cited references. In the event Examiner disagrees, Applicants respectfully request that Examiner provides a citation that supports the Examiner's position.

In response to the Examiner's statement that Friedel teaches "various dosage amounts (such as 1000 mg-1500 mg)," Applicants note that these amounts exceed the per unit amount of active ingredients taught by the Baker reference (i.e., "from about 5 milligrams to about 600 milligrams of active ingredients"). *Baker, column 3, lines 60-61.*

Applicants respectfully request that the arguments presented in the response filed on February 21, 2008 (herein incorporated by reference) be reconsidered in view of the comments above.

For the foregoing reasons, Applicants submit that nabumetone is not an equivalent of ibuprofen and respectfully request withdrawal of the obviousness rejection.

With further regard to new claim 66, it is respectfully submitted that the combination of the cited references does not teach combining oxycodone with 1000 mg of nabumetone, because 1000 mg is outside the range of amounts of active ingredients per unit purportedly taught by Baker (i.e., "a total amount of from about 5 milligrams to about 600 milligrams of active ingredients per unit"). *See Baker, column 3, lines 60-62*

D. 35 U.S.C. § 103 (a) Rejection over Baker et al., Friedel et al. and Eversmeyer et al. in view of Oshlack et al. (US 5,472,712) or Oshlack et al. (US 6,294,195)

Claims 38 and 47-65 were rejected under 35 U.S.C. § 103(a) over the Baker patent, Friedel et al. and Eversmeyer et al., and Oshlack et al. (US 5,472,712) or Oshlack et al. (US 6,294,195).

Applicants submit that, for the reasons discussed above, the cited references do not suggest that nabumetone is safer than ibuprofen and do not provide a reason for one skilled in the art to substitute ibuprofen of the Baker compositions with nabumetone.

With further regard to claim 59, Applicants submit that the combination of the cited references does not suggest a tablet coated with nabumetone in an immediate release form.

Withdrawal of the rejection is respectfully requested.

E. Claim Objections

Claim 57 and 58 were objected to. The Examiner stated that claim 57 recites "said dosage form comprises ... and does not limit the close-ended phrase consisting of" as recited in instant claim 53." *Office Action, page 19.* Claim 58 was objected to for depending from the objected claim 57.

Claim 57 has been amended without prejudice to remove the term "comprises." Amended claim 57 recites "The method of claim 53, wherein said dosage form is in a form of particles having a diameter from about 0.1 mm to about 2.5 mm."

Withdrawal of the objection is respectfully requested.

F. Rejection under 35 U.S.C. § 112

Claim 56 was rejected under 35 U.S.C. § 112, second paragraph. The Examiner stated that "it is not clear if the instant claim language is intended to recite the "said" pain comprise all the different types of pain listed in the instant claims or if the instant claim is reciting a Markush group."

Claim 56 has been amended without prejudice to recite "the selected from the group consisting of" language, which clarifies that the instant claim is reciting a Markush group.

Withdrawal of the objection is respectfully requested.

G. Rejection under 35 U.S.C. § 103(a) over U.S. Patent No. 5,840,731

Claims 38, 47-52 and 60-65 were rejected under 35 U.S.C. § 103(a) over U.S. Patent No. 5,840,731 to Mayer et al., and if necessary in view of Friedel and Eversmeyer.

The rejection is respectfully traversed.

Applicants submit that a dosage form in accordance with the Mayer patent would necessarily include "a nontoxic N-methyl-D-aspartate receptor antagonist," e.g., because the Mayer patent states that "the analgesic effectiveness of known combination drugs containing at least one analgesic drug can be significantly enhanced by the addition of a nontoxic N-methyl-D-aspartate receptor antagonist." *See e.g., column 2, lines 30-34.*

"A nontoxic N-methyl-D-aspartate receptor antagonist" is excluded from the scope of the rejected claims, by virtue of the "consisting of" language recited in claim 38. These claims are not therefore rendered obvious by the combination of the cited references, because the mandatory ingredient of the primary reference (i.e., "a nontoxic N-methyl-D-aspartate receptor antagonist" is excluded from the scope of the present claims.

Applicants further submit that the cited reference do not provide a suggestion for a specific combination of oxycodone and nabumetone as recited in the present claims.

Withdrawal of the rejection is respectfully requested.

III. CONCLUSION

An early and favorable action on the merits is earnestly solicited. The Examiner is respectfully requested to contact the undersigned at the telephone number provided below in the event that a telephonic interview will advance the prosecution of the application.

Respectfully submitted,
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APPENDIX A

FORM PTO-1449 (REV. 7-80) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTY. DOCKET NO.: 200.1079CON4	SERIAL NO.: 10/056,348
LIST OF PRIOR ART CITED BY APPLICANT (Use several sheets if necessary)	APPLICANT(S): Ronald M. BURCH, et al.	
	FILING DATE: January 25, 2002	GROUP: 1639

U.S. PATENT DOCUMENTS

*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	AA						
	AB						
	AC						

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION	
							YES	NO
	AD							
	AE							
	AF							

OTHER PRIOR ART (Including Author, Title, Date, Pertinent Pages, Etc.)

	AG	Degner, Frank, et al., "Efficacy and Tolerability of Meloxicam in an Observational, Controlled Cohort Study in Patients with Rheumatic Disease", Clin Therapeutics (Nov 2000) 22: 400-410.
	AH	Lanes, Stephan et al., "Baseline Risk of Gastrointestinal Disorders Among New Users of Meloxicam, Ibuprofen, Diclofenac, Naaproxen and Indomethacin", Pharmacoepidemiology and Drug Safety (2000) 9:113-117.
	AI	Translation of Office Action dated November 1, 2001, issued in connection with Russian Federation Patent Application No. 2000109552.
	AJ	STN: File Registry printout of Registry Number 162054-19-5 (June 14, 2004).
	AK	Abstract of SANTOS et al., "Antinociceptive effect of meloxicam, in neurogenic and inflammatory nociceptive models in Mice," Inflammation Research (1998), 47(7) pages 302-307, Chem. Abst. Vol. 129 (Columbus, OH)
	AL	FRÖLICH, J.C., "A classification of NSAIDs according to the relative inhibition of cyclooxygenase isoenzymes," TiPS, January 1997, vol. 18, pages 30-34.
	AM	Abstract of OGINO K. et al., "Evaluation of pharmacological profile of meloxicam as an anti-inflammatroy agent, with particular reference to its relative selectivity for cyclooxygenase-2 over cyclooxygenase-1," Pharmacology 55(1):44-53, July 1997.
	AN	Abstract of ISAKSON P. et al., "Discovery of a better aspirin," Advances in Prostaglandin, Thromboxane, & Leukotriene Research 23:49-54, 1995.
	AO	Abstract of JOUZEAU J.Y. et al., "Cyclo-oxygenase isoenzymes. How recent findings affect thinking about nonsteroidal anti-inflammatory drus," Drugs 53(4):563-82, April 1997.
	AP	Abstract of DVORNIK D.M., "Tissue selective inhibition of prostaglandin biosynthesis by etodolac," Journal of Rheumatology, Supplement 47:40-7, February 1997.
	AQ	Richy, F., et al., "Time dependent risk of gastrointestinal complications induced by non-steroid anti-inflammatory drug use: a consensus statement using a meta-analytic approach", Ann Rhuem Dis (2004) 64:759-766.

EXAMINER	DATE CONSIDERED

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

FORM PTO-1449 (REV. 7-80)	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTY. DOCKET NO.: 200.1079CON4	SERIAL NO.: 10/056,348
LIST OF PRIOR ART CITED BY APPLICANT		APPLICANT(S): Ronald M. BURCH, et al.	
(Use several sheets if necessary)		FILING DATE: January 25, 2002	GROUP: 1639

U.S. PATENT DOCUMENTS

*EXAMINER R INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	BA						
	BB						
	BC						

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION	
							YES	NO
	BD							
	BE							

OTHER PRIOR ART (Including Author, Title, Date, Pertinent Pages, Etc.)

	BF	Goodman & Gillman's (1996), The Pharmacological Basis of Therapeutics, 9th Edition, McGraw-Hill, New York, pp. 654-655.
	BG	Abstract of FLOWER R. J., "New directions in cyclooxygenase research and their implications for NSAID-gastropathy," Italian Journal of Gastroenterology, 28 Suppl. 4:23-7, December 1996.
	BH	Abstract of KURUMBAIL R.G. et al., "Structural basis for selective inhibition of cyclooxygenase-2 by anti-inflammatory agents," Nature, 384(6610):644-8, December 19-26, 1996.
	BI	Abstract of HOSIE J. et al., "Meloxicam in osteoarthritis: a 6-month, double-blind comparison with diclofenac sodium," British Journal of Rheumatology, 35 Suppl. 1:39-43, April 1996.
	BJ	Abstract of PAIRET M. et al., "Distinct isoforms (COX-1 and COX-2) of cyclooxygenase: possible physiological and therapeutic implications," Fundamental & Clinical Pharmacology 10(1):1-17, 1996.
	BK	Abstract of MASFERRER J.L. et al, "Cyclooxygenase-2 inhibitors: a new class of anti-inflammatory agents that spare the gastrointestinal tract," Gastroenterology Clinics of North America 25(2):363-72, June 1996.
	BL	Abstract of EMERY P., "Clinical implications of selective cycloxygenase-2 inhibiton," Scandinavian Journal of Rheumatology-Supplement 102:23-8, 1996.
	BM	Van Hecken, Anne, et al., "Comparative Inhibitory Activity of Rofecoxib, Meloxicam, Diclofenac, Ibuprofen, and Naproxen on COX-2 versus COX-1 in Healthy Volunteers", J Clin Pharmacol (2000) 40: 1109-1120.
	BN	
	BO	

EXAMINER	DATE CONSIDERED

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.